

KUSE ET AL

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1. Untranslatable words are replaced with asterisks (\*\*\*\*).
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### [Claim(s)]

[Claim 1] The vitamin constituent characterized by containing a vitamin K and flavonoids.

[Claim 2] The vitamin constituent according to claim 1 characterized by below 50,000 mass parts containing [ more than 30 mass parts ] flavonoids to a vitamin-K1 mass part.

[Claim 3] Flavonoids The quercetin, rutin, hesperidin, hesperitin, Myricetin, quercitrin, FISECHIN, the apigenin, kaempferol, Luteolin, ERIO citrin, CULCON, anthocyanidin, leuco anthocyanidin, The vitamin constituent according to claim 1 or 2 characterized by being one or more kinds chosen from catechin, epicatechin, GAROKATEKIN, epigallocatechin, epicatechin gallate, epigallocatechin gallate, and isoflavone.

[Claim 4] Isoflavone A soybean, soybean hypocotyl, a soybean fermentation thing, a soybean hypocotyl fermentation thing, a red clover, the soybean extract extracted from a kudzu or these each, a soybean hypocotyl extract, a soybean fermentation extract, a soybean hypocotyl fermentation extract, a red clover extract, and a kudzu -- the vitamin constituent according to claim 3 characterized by being contained as one or more kinds of things chosen from the extract.

[Claim 5] The vitamin constituent according to claim 3 characterized by containing catechin, epicatechin, GAROKATEKIN, epigallocatechin, epicatechin gallate, or epigallocatechin gallate as an end of tea powder, or tea extract.

[Claim 6] The vitamin constituent according to claim 3 with which catechin, epicatechin, GAROKATEKIN, epigallocatechin, epicatechin gallate, or epigallocatechin gallate is characterized by drying by distillation and extracting from the xylem of pulse family pegu-catechu.

[Claim 7] the vitamin constituent according to claim 3 characterized by containing hesperidin as an extract of the fruit juice of citrus fruits, pericarp, a seed, or these each.

[Claim 8] the vitamin constituent according to claim 3 characterized by containing rutin as an extract of the fruit of buckwheat noodles, a leaf, or these each.

[Claim 9] Claim 1 which furthermore contains an alkaline material -- the vitamin constituent of any 1 clause of eight.

[Claim 10] The vitamin constituent of Claim 9 whose alkaline material is end of end of sodium, potassium, magnesium or carbonate [ of ammonium ], bicarbonate or hydroxide, edible shell powder, end of petrification seaweed, and coral, and dolomite, or calcination shell powder.

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### [Detailed Description of the Invention]

#### [0001]

[Field of the Invention] This invention relates to the vitamin constituent excellent in stability.

#### [0002]

[Description of the Prior Art] The concern of people who receive healthily in connection with an aging society is strong. The fall of the bone density according [ especially osteoporosis ] to aging causes fracture, distortion of a skeleton, etc., and the pain accompanying it etc. not only causes the fall of QOL (quality of life), but when the worst, it is forced a bedridden life, for example by

fracture of the the femur etc. therefore, also in order to raise QOL of old age, the fall of bone density is controlled, and osteoporosis is prevented -- an owner -- requests for a \*\*\*\* means are mounting increasingly.

[0003] A vitamin K, vitamin D3, estrogen, isoflavone, ipriflavone, calcitonin, screw FOSUFONETO, trehalose, etc. are known by that which prevention and the therapy of osteoporosis are expected that the effect is. It becomes clear that there is work very important for RIMORUDINGU of the functionality over the bone of a vitamin K, i.e., a bone, as nutritional information contained especially in food, and it is a safe osteoporosis-prophylaxis component, Not only use by drugs but the usage in the compound component which aimed at the single component or the synergistic effect in the food field called functional food, health food, and a supplement is considered.

[0004] The side chain of an isoprene derivative takes lessons for a vitamin K from a 1,4-naphthoquinone skeleton, and the vitamin K3 (menadione) which is vitamin K2 (menaquinone) and synthetic compounds which the vitamin K1 (phyloquinone) which vegetation produces, and bacteria produce is. Moreover, about menaquinone, it is classified into MK 1-14 according to the number of isoprene units.

[0005] In food and drugs, since the character of a vitamin K is unstable to light and an alkali, when aiming at vitamin K strengthening, stability of a vitamin K is made into a problem. Although the mixture of calcium etc. and a vitamin K is known especially as osteoporosis-prophylaxis food, Carbonate, such as sodium, potassium, magnesium, and ammonium, bicarbonate, Or the shell powder of natural materials which use calcium carbonate as a principal component, such as a hydroxide, It is combining with a vitamin K alkaline materials, such as materials in the end of petrification seaweed etc., or a material which used calcium oxide like calcination shell powder as the principal component, and it is known in the end of a dolomite in the end of coral that stability will get much more bad.

[0006] In the case of processing of a tablet as conventional ways of coping the method of carrying out trituration only of the vitamin K by excipients, such as cellulose, and mixing back to the agglomerated material of an alkaline material and other excipients, and tableting to it -- it is (food, development, vol34, No.4, P40-42) -- the temporal stability of a vitamin K cannot fully be solved.

[0007] Moreover, the fats-and-oils coat method which generally carries out the heating dissolution of the lipid nature substance at an organic solvent, and carries out spray drying of the solution on the surface of a principal component, Or the fats-and-oils coat method (patent No. 1479697, JP, H3-58264, B, patent No. 2729494) of not using an organic solvent, and the method of applying the technology of a microcapsule (patent No. 1002105) etc. further, carrying out the coat of the vitamin K, and attaining stabilization are also considered.

[0008] However, hydrocarbons, such as halogenated hydrocarbon, such as the organic solvent with which the fats-and-oils coat method using an organic solvent is generally used widely, for example, carbon tetrachloride, and chloroform, hexane, and benzene, lower alcohol, acetone, etc. require very much time, in order to carry out desiccation elimination of these completely. Moreover, even if toxicity is low, when using an inflammable solvent, it is, [ organic solvent / with the toxicity of a hydrocarbon, halogenated hydrocarbon, etc. strong in explosion-proof equipment being needed from the field of disaster prevention ] In order to plan environmental contamination prevention by the organic solvent exhausted [ were exhausted, and were exhausted, and, or it evaporated ], there are many problems, like great plant-and-equipment investment is needed: [ which prevents the disclosure to the work environment at the time of manufacture and maintains a worker's safe sanitation ]

[0009] The manufacturing method of the sustained release drug offered as how not to use an organic solvent, on the other hand (patent No. 1479697, JP, H3-58264, B, patent No. 2729494), as the lipid nature substance furthermore used in the manufacturing method (patent No. 1002105) of a microcapsule, respectively -- higher alcohols, a higher fatty acid group, higher fatty acid glycerol ester, a hardened oil, and wax -- although a kind, a hydrocarbon, etc. are raised For example, relevance with the risk of a circulatory system disease is suggested in Europe and America, and it is not appropriate for a hardened oil to use it as the health food taken in every

day or an additive to pharmaceutical preparation. About the vitamin K1 (phylloquinone) whose fusing point is -20 degree C, and vitamin K2 (menaquinone) whose fusing point is 54 degrees C, such technology has fully come [ it is necessary to mix with the lipid nature substance used, respectively under the temperature conditions more than the fusing point, and / furthermore, ] to be put in practical use.

[0010] Moreover, although a thing and the microcapsule according to gelatin etc. further using a cellulosic, a natural polysaccharide, zein, gelatin, etc. as the coat methods other than a fats-and-oils coat are also known A manufacturing process increases [ that great expense starts plant-and-equipment investment when using an organic solvent similarly or that drying time takes time, and ] further. When cost is made to add and the amount of active principles is blended, in order to use it for the purpose of nutrient enrichment to the pharmaceutical preparation or food in the last form, there is a problem of becoming a cost overrun.

[0011]

[Problem(s) to be Solved by the Invention] Although the vitamin K is comparatively stable to heat, air oxidation, and a dilute acid, it is unstable to light. Moreover, when it is processed into food and drugs, and it combines with an alkaline material especially, the stability poses [ since it was dramatically unstable to an alkali, ] a problem. The purpose of this invention is to offer the vitamin K constituent which canceled these faults and was excellent in stability.

[0012]

[Means for Solving the Problem] This invention persons were making a vitamin K contain flavonoids, found out that the stability of a vitamin K was improved and resulted in this invention. That is, this invention is a vitamin constituent characterized by containing a vitamin K and flavonoids.

[0013] [ the rate of a compounding ratio of a vitamin K and flavonoids in this invention ] In more than 30 mass parts, flavonoids to a vitamin-K1 mass part preferably Below 50,000 mass parts Still more preferably, preferably, more than 100 mass parts are below 50,000 mass parts, and more than 50 mass parts can obtain [ below 50,000 mass parts ] especially the vitamin K constituent stabilized especially in this range. In combination with an alkaline material like the calcium which carried out especially carbonate to the rates of a compounding ratio of the flavonoids to a vitamin-K1 mass part being under 30 mass parts with the principal component, or a magnesium material, the effect of this invention becomes weak. Moreover, if the rate of a compounding ratio of flavonoids exceeds 50,000 mass parts, bitterness, astringency, etc. originating in flavonoid will come out strongly.

[0014] With the vitamin K as used in the field of this invention, vitamin K1 (phylloquinone), vitamin K2 (menaquinone), Any of one sort or two sorts or more of mixtures which are chosen from vitamin K3 (menadione) are sufficient, and whichever it uses [ of a natural product and a compound ] it as a vitamin K, the effect of this invention does not change. As a process of a concrete vitamin K, it is vitamin K1, for example. An organic solvent extracts from deep yellow vegetables, a soybean, etc., this is extractives-ized, or excipients, such as starch, dextrin, and zein, an adsorbent, etc. are added to this, and there is the method of carrying out the pulverization by a suitable means. Moreover, vitamin K2 is mainly manufactured by the bacterial coupling by a microorganism, for example, cultivates a BUREBI bacterium, and there is a method of carrying out extraction refining of vitamin K2 produced or a way an organic solvent refines after extraction the deodorization distillate which carries out subraw by the purification process of vegetable oil and fat. A synthetic process uses reduction type vitamin Ks as starting material, and dissolve this in organic solvents, such as isopropyl ether, and add the alkaline water solution adjusted with an alkali and water, oxygen is made to introduce and react under churning, and the method of obtaining a vitamin K etc. is known.

[0015] The flavonoids used by this invention are kinds of phenols, and flavone or a flavanone skeleton, an isoflavone skeleton, etc. which have C6-C3-C6 mechanism fundamentally are made into the basic skeleton. As a concrete example, the quercetin, rutin, hesperidin, hesperitin, Myricetin, quercitrin, FISECHIN, the apigenin, kaempferol, There are luteolin, ERIO citrin, CULCON, anthocyanidin, leuco anthocyanidin, catechin, epicatechin, GAROKATEKIN, epigallocatechin, epicatechin gallate, epigallocatechin gallate, isoflavone, etc. Moreover, it is the

method of aglycon, glycoside or enzyme treatment, or others which is used as flavonoids, and it may be generated. These may be independent or may be used together two or more sorts.

Although typical flavonoids are explained below, it is not limited to this.

[0016] For example, isoflavone, and glycitin, genistin, daidzin, glycitein, genistein, daidzein, 6''-O-acetyldaidzin, 6''-O-malonyldaidzin, 6''-O-acetylglycitin, 6''-O-malonylglycitin, 6''-O-acetylgenistin, 6''-O-maronylgenistin, Biochanin A (methoxygenistein), Formononetin (methoxydaidzein), etc., [ with moreover, the fermentation of that to which these were carried out by microbial fermentation in a certain modification of succinylation, hydroxylation, etc., for example, a natto fungus, ] Things which embellished these by the method of enzyme treatment or others, such as daidzin, glycitin, genistin, etc. which carried out succinylation, are mentioned.

[0017] As a common isoflavone material, what more than 0.1 mass % contains at least is desirable as the total amount of isoflavone. For example, the thing which dried and ground the soybean, the soybean hypocotyl, the red clover, and \*\*\*\*\* containing many isoflavone as it was, Or the thing which passed through the extraction process from them, and was separated and refined, Or a soybean, soybean hypocotyl, a red clover, a kudzu, etc. are dried and ground, and there are some which passed through the extraction process etc. from the thing which carried out the pulverization of what was fermented by aspergilli, such as a microorganism, for example, a natto fungus, or a black koji bacillus, and the Monascus pilosus bacillus, the Aspergillus oryzae bacillus, by the suitable means, or them, and were separated and refined.

[0018] Moreover, hesperidin and rutin are also called vitamin P. Generally hesperidin is extracted, refined and obtained by organic solvents, such as water or ethanol, from the pericarp of citrus fruits, such as a Satsuma mandarin and a grapefruit, fruit juice, and a seed. On the other hand, rutin is extracted and refined by water, ethanol, etc. from the entire plant of the entire plant of department Sova of DADE or the flower of a pulse family Japanese pagoda tree, a bud, or a pulse family azuki bean etc. Moreover, what water-soluble hesperidin and the water-soluble rutin which are obtained by embellishing hesperidin and rutin by the method of enzyme treatment or others could be used, hesperidin ground the pericarp of citrus fruits,/, and a sowing child, and rutin ground the fruit and/or buckwheat-noodles leaf of buckwheat noodles further, and carried out the pulverization may be used.

[0019] Moreover, catechin is dried by distillation, for example from the xylem of pulse family pegu-catechu, the leaf of Theaceae CHA, etc., it is what carried out extraction refining by water or ethanol, and what removed caffeine may be used for it if needed. Moreover, you may be epicatechin, GAROKATEKIN, epigallocatechin, epicatechin gallate, epigallocatechin gallate, etc., and it is independent or two or more sorts of these can be used together.

[0020] In this invention, when an alkaline material is included, the effect can be demonstrated more notably. With an alkaline material, for example Carbonate, such as sodium, potassium, magnesium, or ammonium, There are some which used calcium oxide like calcination shell powder, such as the end of a dolomite, as the principal component in the end of coral in the edible shell powder originating in the scallop which uses calcium carbonate, such as bicarbonate or a hydroxide, as a principal component, an oyster, etc., and the end of petrification seaweed. there being no restriction in \*\* as the quantity, or receiving a flavonoids 1 mass part, for example -- a 0.05 - 50,000 mass part -- desirable -- further -- desirable -- a 0.5 to 25,000 mass part -- a 2.5 - 22,500 mass part is especially preferably good. If it is this range, the stability of a vitamin K will be especially kept good. Uniform dispersion of the alkaline material which specific gravity generally tends to condense heavily at the time of mixing as an alkaline material is under 0.05 mass part becomes difficult. Moreover, if 50,000 mass parts are exceeded, the effect of this invention will tend to become weak.

[0021] Although it is indispensable in this invention to contain a vitamin K and flavonoids In addition to these, if needed An anti-oxidant, for example, vitamin E, the Goma extract, Tannin, the component validated as phenols and other antioxidants, A food additive, the component permitted on medicine manufacture, medicine manufacture, the lactose used with food, You may contain excipients, such as malt sugar, grape sugar, cane sugar, reduction malt sugar, recombined milk sugar, trehalose, erythritol, xylitol, sorbitol, mannitol, cellulose, starch, a cellulosic, and dextrin, an adsorbent, a coloring agent, perfume, etc.

[0022] That with which the vitamin constituent of this invention mixed other additives a vitamin K, flavonoids, and if needed, Or these end of mixed powder can be granulated by means represented by churning granulation, fluid bed granulation, and extrusion granulation, such as wet granulation and other dry granulation, for example, and can be obtained easily. Moreover, it is also processible into a tablet, a hard capsule, a soft capsule, etc. as it is the end of these end of mixing, or granulation.

[0023]

[Example] This invention is not limited by these although a concrete work example is given and explained about the effect of this invention below. In addition, the valuation method is as follows.

(1) The aluminum bag with a light sheilding was filled up with the granulation processed under 40 degrees C and 75%RH conditions, respectively, and a tablet about accelerated test each work example and a comparative example, under 40 degrees C and 75%RH conditions, the accelerated test was done for three months and the amount of vitamin Ks was measured.

(2) The vitamin K concentration three months and at the time of carrying out room temperature preservation for one year was measured with the aluminum bag with the light sheilding the long-term storage test work example 7, a comparative example 4, and per five.

[0024] Vitamin K2 used that by which extraction refining was carried out with bacterial coupling in the end of extractives work examples 1-6 and the vitamin K1 used comparative example 1-3 carried out ethanol extraction from celery. Isoflavone, hesperidin, and green tea catechin were chosen and used as flavonoids. The end of extractives it extracted and refined from soybean hypocotyl was used in the end of extractives it extracted and refined from the fermentation thing which the soybean was fermented with the black koji bacillus and carried out the pulverization as isoflavone. As hesperidin, Sunphenon 100S of TAIYO KAGAKU CO., LTD. and the Sanka torr were used as the thing of Alps Pharmaceutical industry, and catechin. In each work example and a comparative example, based on the combination formula of Table 1, the ethanol aqueous solution was sprayed 70% after mixing each material, churning granulation was performed, suction drying was performed for 50 degrees C and 3 hours, and the particle size regulation and the granulated thing were used as it was. The preservation result by an accelerated test is shown in Table 2 by residual ratio. Good stability was acquired in the work examples 1-6 which blended with the vitamin K isoflavone, catechin, and hesperidin which are flavonoids.

[0025]

[Table 1]

表1 配合処方(質量%);顆粒

	実施例 1	実施例 2	実施例 3	実施例 4	実施例 5	実施例 6	比較例 1	比較例 2	比較例 3
ビタミンK <sub>1</sub>	0.1								
ビタミンK <sub>2</sub> 倍散		0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
大豆胚軸エキス	0.125	0.125							
大豆発酵エキス			0.25						
ヘスペリジン				0.5					
ビタミンE								0.5	
ビタミンC									0.5
サンプェノール100S					0.5				
サンカトール						0.5			
ドロマイト	50	50	50	50	50	50	50	50	50
還元麦芽糖	20	20	20	20	20	20	20	20	20
セルロース	29.775	29.87	29.745	29.495	29.495	29.495	29.995	29.995	29.495
合計	100	100	100	100	100	100	100	100	100

\*ビタミンK<sub>1</sub>は、0.01%倍散末、ビタミンK<sub>2</sub>倍散は、0.2%倍散末、大豆胚軸エキスは総イソフラボン量として40%含有のエキス末、大豆発酵エキスは、総イソフラボン(アグリコン)量として20%含有のエキス末を使用した。

\*サンプェノール100S(茶抽出物;ポリフェノール含量78%、カテキン2.8%)

\*サンカトール(ビタミンEと茶抽出物ミックス;ポリフェノール含量7.8%、カテキン含量0.28%、抽出トコフェロール含量9%)

[0026]

[Table 2]

表2 残存率(%)

	加速試験
実施例1	94
実施例2	91
実施例3	110
実施例4	100
実施例5	92
実施例6	110
比較例1	58
比較例2	70
比較例3	60

[0027] Based on the combination formula of work-examples 7-8 and comparative example 5 table 3, it granulated like the work example 1, and this was processed into the tablet. The result of the accelerated test and the long-term storage test was shown in Table 4 by residual ratio. In the work examples 7 and 8, all three conditions showed stability better than a comparative example 4. As for some effects of this invention, the weak trend was seen, although the work example 8 with few flavonoids contents had blended isoflavone, the residual ratio of one year after was low as compared with the work example 7 and stability was clearly superior to the comparative example 4.

[0028]

[Table 3]

表3 実施例及び比較例の組成(質量%) ; 錠 剤

	実施例 7	実施例 8	比較例 4
ビタミンK <sub>2</sub>	0.00045	0.00090	0.00045
大豆胚軸エキス 10	0.5	0.25	0
未焼成貝殻粉	40	40	40
卵殻粉	10	10	10
還元麦芽糖	30	30	30
セルロース	14.49955	14.7491	14.99955
シュガーエステル	1	1	1
植物油脂末	2	2	2
グアーガム	2	2	2
合計	100	100	100

\*ビタミンK<sub>2</sub>は、純度 100%の原末を使用した。

\*大豆胚軸エキス 10 は総イソフラボン量として 10%含有エキスを使用した。

[0029]

[Table 4]

表4 残存率 (%)

	加速試験	長期保存試験	
		3ヶ月	1年
実施例 7	94	98	95
実施例 8	87	96	78
比較例 4	78	90	68

[0030]

[Effect of the Invention] As mentioned above, the problem of the stability produced with combination with an alkaline material after processing of a vitamin K was able to be solved by this invention, and the vitamin constituent excellent in stability was able to be obtained.

[Translation done.]